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(54) Title: PREPOLYMER COMPOSITIONS COMPRISING AN ANTIMICROBIAL AGENT

(57) Abstract

Disclosed are biocompatible prepolymer compositions comprising a compatible antimicrobial agent. These compositions provide for *in situ* formation of an antimicrobial polymeric film on mammalian skin.

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PREPOLYMER COMPOSITIONS COMPRISING AN ANTIMICROBIAL AGENT

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is directed to prepolymer compositions comprising a compatible antimicrobial agent. These compositions provide for *in situ* formation of antimicrobial polymeric films on mammalian skin which films are useful as wound dressings, wound bandages, surgical incise drapes, wound closure materials which replace or are an adjunct to sutures, and the like.

This invention is also directed to kits of parts comprising such prepolymer compositions and an applicator means for applying the composition to mammalian skin.

References

The following publications, patent applications and patents are cited in this application as superscript numbers:

[1] Hawkins, et al., "*Surgical Adhesive Compositions*", U.S. Patent No. 3,591,676, issued July 6, 1971

[2] Halpern, et al., "*Adhesive for Living Tissue*", U.S. Patent No. 3,667,472, issued June 6, 1972

[3] Blum, et al., "*In vitro Determination of the Antimicrobial Properties of Two Cyanoacrylate Preparations*", J. Dent. Res., 54(3):500-503 (1975)

[4] Barley, et al., "*Methods for Treating Non-Suturable Wounds by Use of Cyanoacrylate Adhesives*", International Patent Application Publication No. WO 93/25196, published December 23, 1993

[5] Barley, et al., "*Methods for Treating Suturable Wounds by Use of Sutures and Cyanoacrylate Adhesives*", U.S. Patent No. 5,254,132, issued October 19, 1993

[6] Khan, et al., "*Preparation of a Skin Surface for a Surgical Procedure*", U.S. Patent No. 5,547,662, issued August 20, 1996

[7] Byram, et al., "*Methods to Inhibit Acute Radiation Induced Skin Damage*", International Patent Application Publication No. WO 96/34610, published November 7, 1996.

[8] Cardarelli, et al., "*Film Forming Antimicrobial Material*", U.S. Patent No. 4,374,126, issued February 15, 1983

[9] Askill, et al., "*Methods for Draping Surgical Incision Sites Using a Biocompatible Prepolymer*", U.S. Patent Application Serial No. 08/941,097 filed October 8, 1997 as Attorney Docket No. 026446-108

[10] Dell, "*Film-Forming Composition Containing an Antimicrobial Agent and Methods*", U.S. Patent No. 4,542,012, issued September 17, 1985

[11] Greff, et al., "*Prepolymer Compositions Comprising an Anti-Microbial Agent*", U.S. Patent Application Serial No. 08/947,109 filed October 8, 1997 as Attorney Docket No. 026446-087

[12] Brink, et al., "*Film-Forming Emulsion Containing Iodine and Methods of Use*", U.S. Patent No. 5,173,291, issued December 22, 1992

[13] Hagen, et al., "*A Comparison of Two Skin Preps Used in Cardiac Surgical Procedures*", AORN Journal, 62(3):393-402 (1995)

[14] Ritter, et al., "*Retrospective Evaluation of an Iodophor-Incorporated Antimicrobial Plastic Adhesive Wound Drape*", Clinical Orthopedics and Related Research, pp. 307-308 (1988)

[15] Osuna, et al., "*Comparison of an Antimicrobial Adhesive Drape and Povidone-Iodine Preoperative Skin Preparation in Dogs*", Veterinary Surgery, 21(6):458-462 (1992)

[16] Matsumoto, "*Chapter 3: Bacteriology and Wound Healing*", in "Tissue Adhesives in Surgery", Medical Examination Publishing Company, Inc., Flushing, New York, USA, pp. 106-113 (1972)

[17] Modern Plastics Encyclopedia, 1997

[18] Mixon, "*Surgical Drape having Incorporated therein a Broad Spectrum Antimicrobial Agent*", U.S. Patent No. 5,069,907, issued December 3, 1991

[19] Greff, et al., "*Methods and Compositions for Treating Dermatoses*" U.S. Patent Application Serial No. 08/963,265 filed concurrently herewith as Attorney Docket No. 026446-067

[20] "*Kits Containing Cyanoacrylate Compositions Comprising an Antimicrobial Agent*", U.S. Patent Application Serial No. 08/962,869, filed concurrently herewith as Attorney Docket No. 026446-111

All of the above publications, patent applications and patents are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent application or patent was specifically and individually indicated to be incorporated by reference in its entirety.

State of the Art

Biocompatible prepolymer compositions, such as compositions comprising cyanoacrylate esters, have been disclosed for a variety of topical uses on mammalian skin including use as a replacement or adjunct for sutures or staples in closing the dermal layer of an incision after surgery.[1,2,5] Other disclosed topical uses of such prepolymer compositions include inhibition of acute radiation-induced skin damage[7] as well as in the *in situ* formation of a surgical incise drape.[9] Other suitable prepolymer compositions include compositions comprising prepolymers other than cyanoacrylate and povidone-iodine.[11]

In each case, when topically applied to mammalian skin, the biocompatible prepolymer composition polymerizes to form a coherent polymeric film which adheres to the skin.

Notwithstanding the beneficial properties associated with such prepolymer compositions and their suitability for topical applications, these compositions do not possess a sufficiently broad and/or active spectrum of antimicrobial activity including activity against microbial spores and, accordingly, cannot assure reductions in microbial populations on mammalian skin surface either under or adjacent the polymeric film formed *in situ* on the skin.[3,16]

Many of the uses of prepolymer compositions enumerated above would, however, significantly benefit by an antimicrobial property in the polymer film. For instance, when used as a surgical (incise) drape, such films would reduce microbial populations under and adjacent the drape including those at the incision site and, accordingly, would reduce the risk of post-operative infection. Such is the basic premise of commercial surgical drapes containing an antimicrobial agent impregnated directly into the drape or in an adhesive layer attached thereto where it was hoped that this agent would be released onto the skin surface to inhibit microbial growth.[13,14] Osuna, et al.[15] report, however, that

when the antimicrobial agent is incorporated into the adhesive layer, the adhesive does not release sufficient amounts of the impregnated agent to be, by itself, antimicrobial. Without being limited to any theory, it is believed that the antimicrobial agent is too strongly bound onto/into the adhesive to be released onto the skin and/or that there is insufficient skin surface contact between the adhesive and the skin to effect release of a sufficient amount of antimicrobial agent.

As noted above, most prepolymer compositions do not possess antimicrobial activity and, accordingly, *in situ* formation of a polymeric film on mammalian skin which film possesses antimicrobial properties necessitates, of course, that an antimicrobially effective amount of an antimicrobial agent be incorporated into the prepolymer composition and that sufficient amounts of this agent be released from the polymeric film onto the skin to achieve an antimicrobial effect. The incorporation of such an antimicrobial agent into the composition is problematic at best because several disparate criteria must be simultaneously met. First, the antimicrobial agent must be soluble or dispersible in the prepolymer composition at the concentrations necessary to effect antimicrobial properties. Second, the antimicrobial agent employed must not cause premature polymerization of the prepolymer composition. Third, the antimicrobial agent employed must not prevent *in situ* polymerization of the prepolymer composition when applied to the skin. Fourth, the antimicrobial agent must be compatible with the intended use of the polymeric film by not inhibiting formation of a flexible, durable film. Fifth, the impregnated antimicrobial agent must be released from the polymerized film *in situ* on the patient's skin in sufficient amounts to be antimicrobial.

Because of these disparate properties, antimicrobial agents have not been incorporated into prepolymers but, rather, solutions or emulsions of the formed polymer are employed and these solutions/emulsions are then applied to the patient's skin. In such cases, subsequent evaporation of the solvent leaves a polymer film on the skin which film is permeated with the antimicrobial agent.[8,10,12] Alternatively, the antimicrobial agent may be incorporated into a polymer melt[18] and then extruded as a film which is applied to the skin. Since the polymer is preformed prior to application to the skin, these solutions/emulsions reduce the effective adherence of the polymer film to the skin and, accordingly, could lead to premature lifting or removal of the film from the skin.

Moreover, the use of water and other solvents in the emulsion or solution leads to slow drying times for the film with the concurrent difficulty in determining when or if the solvent has evaporated sufficiently to provide a polymer film on the patient's skin.[6] Replacement of water in such aqueous formulations with a quick drying organic solvent such as acetone, isopropanol, etc. leads to noxious/flammable vapors in the operating room and, in many cases, these solvents cause skin irritation. In any event, the use of such emulsions or solutions requires application of relatively large quantities of these compositions onto the skin in order to account for the portion which evaporates therefrom.

Still, in another alternative, commercially available embodiment (e.g., IOBAN™), a polymeric film is coated with an adhesive layer having an antimicrobial agent incorporated into the adhesive. Such films, however, suffer from poor contact of the adhesive layer with the skin and subsequently reduced antimicrobial effects. Additionally, notwithstanding the use of the adhesive, the polymeric film can lift during surgical procedures which has an adverse effect on infection rates.[15]

In addition, there is a need for a polymeric film with an antimicrobial aimed at prevention or treatment of specific dermatological problems. An example of this need is the requirement for antifungals in topical products used for incontinence, where the incidence of fungal infection is extremely high.

In view of the clear benefits associated with the incorporation of an antimicrobial agent directly into the prepolymer composition, there is an ongoing need to formulate a prepolymer composition comprising an antimicrobial agent, mixtures of antimicrobials and specific therapeutic antimicrobials.

SUMMARY OF THE INVENTION

This invention is directed to prepolymer compositions comprising a polymerizable biocompatible prepolymer composition and an antimicrobially effective amount of an antimicrobial agent. These compositions provide for *in situ* formation of an antimicrobial polymeric film on mammalian skin. The specific antimicrobial employed is compatible with the prepolymer composition insofar as the antimicrobial neither causes

premature polymerization nor prevents polymerization, rather a flexible, adhesive and durable polymer film is formed *in situ* on mammalian skin by this composition. Moreover, the antimicrobial agent is expected to be released from the polymeric film in antimicrobially effective amounts thereby imparting antimicrobial properties to the polymeric film.

Accordingly, in one of its composition aspects, this invention is directed to an antimicrobial prepolymer composition which comprises:

(a) a polymerizable biocompatible prepolymer composition; and

(b) an antimicrobially effective amount of an antimicrobial agent with the proviso that the biocompatible prepolymer composition is neither a cyanoacrylate prepolymer composition nor a silicone prepolymer composition and the antimicrobial agent is not a complex of iodine molecules.

Preferably, the polymerizable biocompatible prepolymer composition is selected from the group of prepolymers consisting of urethane acrylate, (C_1-C_6 alkyl) (C_1-C_6) alkacrylate (e.g., methyl methacrylate), (C_1-C_6 alkyl) acrylate, (C_1-C_6 hydroxyalkyl) acrylate, (C_1-C_6 hydroxyalkyl) alkacrylate, styrene, α-methyl styrene, vinyl acetate, one and two component epoxy materials, mixtures thereof, and the like.

Antimicrobial agents include, by way of example, antibacterials, antifungals, antibiotics, antivirals and antiparasitics. Preferably, such antimicrobial agents are selected from the group consisting of acyclovir, amphotericin B, bacitracin, butoconazole nitrate, carbol-fuchsin solution, chloramphenicol, chlortetracycline hydrochloride, ciclopirox olamine, clindamycin phosphate, clotrimazole, econazole nitrate, erythromycin, gentamycin sulfate, gentian violet, haloprogin, iodochlorhydroxyquin, ketoconazole, mafenide acetate, metronidazole, miconazole nitrate, mupirocin, naftifine, neomycin sulfate, nitrofurazone, nystatin, oxiconazole nitrate, silver sulfadiazine, sulconazole nitrate, tetracycline hydrochloride, tolnaftate, undecylenic acid and zinc undecylenate, benzyl benzoate, crotamiton, lindane, permethrin, pyrethrins, quaternary ammonium compounds, e.g., cetrimide, biguanide compounds such as chlorhexidine and its salts, e.g., chlorhexidine gluconate, and chlorophenols, e.g. MICROBAN® (Microban Products).

Preferred antimicrobial agents are chlorhexidine and its salts, neomycin sulfate, bacitracin, miconazole nitrate, naftifine, acyclovir and lindane.

The antimicrobial prepolymer compositions may further comprise an effective amount of a polymerization inhibitor, a biocompatible plasticizer, and a polymerization initiator.

This invention is also directed to a kit of parts useful for applying the antimicrobial prepolymer compositions described herein onto mammalian skin. In particular, such a kit of parts comprises (a) a container comprising therein an antimicrobial prepolymer composition as described above and (b) an applicator means for applying the composition onto mammalian skin.

This invention is also directed to a kit of parts which comprises the prepolymer stored in a first container and the antimicrobial agent stored in a second container. At the appropriate point in time the contents can be mixed together to form the composition described above. Preferably, the first or second container comprises an applicator means such that upon mixing of the components the composition can be applied to mammalian skin. Alternatively, a separate applicator means can be employed in the kit. In a further embodiment the kit may comprise further containers containing additional components.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention is directed, in part, to biocompatible prepolymer compositions comprising a polymerizable biocompatible prepolymer and an antimicrobially effective amount of an antimicrobial agent. However, prior to discussing this invention in further detail, the following terms will first be defined.

Definitions

As used herein, the following terms have the following meanings:

The term "polymerizable biocompatible prepolymer compositions" refer to polymerizable monomers, oligomers or mixtures thereof including single or multi-component systems. The prepolymer composition will polymerize *in situ* on mammalian skin to form an adherent, water-insoluble polymeric layer over the skin. The prepolymer and resulting polymeric film are biocompatible with the skin as measured by the lack of

moderate to severe skin irritation and the resulting polymer film is substantially non-toxic and can be removed from the skin by conventional means, e.g., sloughing off with the epidermal layer of the skin or by removal with a suitable biocompatible solvent (e.g., acetone and isopropanol).

Included within the term "polymerizable biocompatible prepolymer compositions" are both single and multi-component systems. Single component prepolymer compositions include those wherein a single prepolymer is capable of polymerizing under suitable polymerization conditions (e.g., free radical conditions) to provide for a polymer film on mammalian skin. Such single component systems include well known reactive vinyl groups which form a biocompatible polymer such as urethane acrylate, (C_1-C_6 alkyl) (C_1-C_6 alkacrylate, (C_1-C_6 alkyl) acrylate, (C_1-C_6 hydroxyalkyl) acrylate, (C_1-C_6 hydroxyalkyl) alkacrylate, styrene, α-methyl styrene, vinyl acetate, mixtures thereof, and the like. Specific examples of such single component systems include methyl methacrylate, hydroxyethyl methacrylate, styrene, and the like. Additionally, such single component systems can also comprise polymerization inhibitors, polymerization initiators, colorants, perfumes, etc.

Multi-component prepolymer compositions include those wherein two or more components are employed to co-react under suitable polymerization conditions to provide for a polymer film on mammalian skin. An example of a two component system is a diepoxide and a diamine specifically exemplified by bis-phenol A diglycidyl ether and ethylene diamine.

Preferred prepolymers for use in this invention include, by way of example only, urethane acrylate, (C_1-C_6 alkyl) methacrylate, (C_1-C_6 alkyl) acrylate, (C_1-C_6 hydroxyalkyl) acrylate, (C_1-C_6 hydroxyalkyl) alkacrylate, styrene, α-methyl styrene, vinyl acetate, one and two component epoxy materials, mixtures thereof, and the like.

Specifically excluded from the compositions of this invention are prepolymers comprising an iodine containing antimicrobial agent. Such prepolymer compositions are described in commonly assigned U.S. Patent Application Serial Nos. 08/912,681, filed on August 18, 1997, and 08/947,109 filed on October 8, 1997 as Attorney Docket No. 026446-087 and entitled "Prepolymer Compositions Comprising an Antimicrobial Agent

both of which are incorporated herein by reference in their entirety. Also excluded are silicone prepolymers.

The polymerizable biocompatible prepolymer compositions described herein polymerize on mammalian skin tissue without causing histotoxicity or cytotoxicity.

The term "antimicrobial agent" refers to agents which destroy microbes (i.e., bacteria, fungi, viruses, parasites, microbial spores, and the like) thereby preventing their development and pathogenic action. Preferred antimicrobial agents include, by way of example, antibacterials, antifungals, antibiotics, antivirals and antiparasitics.

Examples of suitable antimicrobial agents include acyclovir, amphotericin B, bacitracin, butoconazole nitrate, carbol-fuchsin solution, chloramphenicol, chlortetracycline hydrochloride, ciclopirox olamine, clindamycin phosphate, clotrimazole, econazole nitrate, erythromycin, gentamycin sulfate, gentian violet, haloprogin, iodochlorhydroxyquin, ketoconazole, mafenide acetate, metronidazole, miconazole nitrate, mupirocin, naftifine, neomycin sulfate, nitrofurazone, nystatin, oxiconazole nitrate, silver sulfadiazine, sulconazole nitrate, tetracycline hydrochloride, tolnaftate, undecylenic acid and zinc undecylenate, benzyl benzoate, crotamiton, lindane, permethrin, pyrethrins, quaternary ammonium compounds, e.g., cetrimide, biguanide compounds such as chlorhexidine and its salts, e.g., chlorhexidine gluconate, and chlorophenols, e.g. MICROBAN® (Microban Products).

The term "biocompatible plasticizer" refers to any material which is soluble or dispersible in the prepolymer composition and does not adversely affect the polymerization of the prepolymer when applied to the skin, which increases the flexibility of the resulting polymer film coating on the skin surface, and which, in the amounts employed, is compatible with the skin as measured by the lack of moderate to severe skin irritation. Suitable plasticizers are well known in the art and include those disclosed in Modern Plastics Encyclopedia, 1997[17], the disclosure of which is incorporated herein by reference in its entirety. Specific plasticizers include, by way of example only, citrate plasticizers, phthalate plasticizers, and the like.

The term "polymerization inhibitor" refers to well known free radical inhibitors of prepolymers including materials such as hindered phenols, hydroquinone, 4-methoxyphenol, amines and the like. The polymerization inhibitor is typically employed

in amounts effective to inhibit polymerization of the prepolymer composition until application of the composition onto the mammalian skin and initiation of polymerization as herein described. Preferably, the polymerization inhibitor is employed from about 0.01 to about 0.1 weight percent based on the total weight of the composition.

The term "initiator" refers to those well known polymerization initiators which are typically incorporated into the composition to initiate polymerization of the prepolymer. Such initiators include, by way of example, thermal initiators, light activated (e.g., UV) initiators, and the like. Examples of thermal initiators include peresters, peroxycarbonates, peroxides, azonitrile compounds, and the like. Promoters or accelerators such as metal salts and amines may be used with the initiators. The specific thermal initiator is preferably selected to initiate polymerization of the prepolymer at ambient skin temperatures (e.g., ~35°C) or slightly above with additional heating.

Examples of light activated initiators include benzoin alkyl ethers, benzophenone, Darocur 1173 (available from Ciba Geigy, Ardsley, New York, USA), camphorquinone, and the like.

Preferably, the initiator is a light activated initiator and, after application of the prepolymer composition to mammalian skin, a light source is passed over the skin to initiate polymerization. Even more preferably, the light activated initiator is biocompatible with the skin as measured by the lack of moderate to severe skin irritation.

Compositions

This invention is based on the novel and unexpected discovery that the antimicrobial agents described herein are compatible with prepolymer compositions forming a composition which, upon polymerization, provides for an antimicrobial polymeric film. Compatibility is assessed by the fact that these antimicrobial agents are dispersible or soluble in the prepolymer composition at antimicrobially effective concentrations and when so employed, do not cause premature polymerization of the prepolymer composition and do not prevent effective polymerization of the prepolymer composition when applied to mammalian skin. Moreover, the polymerizable prepolymer composition comprising such antimicrobial agents forms a flexible, durable polymer film

having the antimicrobial agent incorporated therein which antimicrobial agent will release in sufficient amounts to provide antimicrobial properties to the film.

The compositions of this invention are prepared by adding an antimicrobial agent to the prepolymer. The antimicrobial agent is preferably added to the prepolymer as a powder and is dispersed or dissolved in the prepolymer composition. Mixing is employed to obtain a homogeneous solution or suspension. It is understood that the order of addition is not critical.

The amount of antimicrobial agent added to the composition is a sufficient amount such that the resulting polymeric film is antimicrobial. Preferably, from about 0.5 to about 30 weight percent of the antimicrobial agent and more preferably from about 1 to 25 weight percent is added to the composition based on the total weight of the composition.

The specific amount of antimicrobial agent required to effect antimicrobial properties in the resulting polymeric film can be readily measured by conventional *in vitro* assays measuring zones of microbial growth inhibition around the film. Zones of inhibition of at least 1 millimeter and preferably 3 millimeters from the edge of the film when tested in the manner of Example 3 below evidence that the polymeric film is antimicrobial. Assessing the amount of antimicrobial agent required in the polymeric film to effect such a zone of inhibition is well within the skill of the art.

The composition of the antimicrobial and the polymerizable biocompatible prepolymer can be formulated to a specific viscosity to meet disparate demands for the intended application of the composition. For example, relatively low viscosities are often preferred where application is to be made to a large surface area (e.g., abdominal surfaces). This preference results from the fact that these forms are less viscous and, accordingly, will permit more facile large surface area application of a thin film. Contrarily, where application is to be made to a specific position on the skin (e.g., elbow surfaces, knee surfaces and the like), higher viscosity materials are preferred to prevent "running" of the material to unintended locations.

Accordingly, these compositions preferably have a viscosity of from about 10 to 50,000 centipoise at 20°C. For low viscosity applications, viscosity ranges of from about 10 to 1,500 centipoise at 20°C are preferred. More preferably, the biocompatible

prepolymer employed in the composition is almost entirely in monomeric form and the composition has a viscosity of from about 10 to about 500 centipoise at 20°C.

A thickening agent is optionally employed to increase the viscosity of the composition which thickening agent is any biocompatible material which increases the viscosity of the composition. Suitable thickening agents include, by way of example, polymethyl methacrylate (PMMA), polymers of the respective prepolymer or other preformed polymers soluble or dispersible in the composition, a suspending agent such as fumed silica and the like. Fumed silica is particularly useful in producing a gel for topical application having a viscosity of from about 1500 to 50,000.

Thickening agents are deemed to be biocompatible if they are soluble or dispersible in the composition and are compatible with the skin as measured by the lack of moderate to severe skin irritation.

The prepolymer compositions of this invention can optionally include a biocompatible plasticizer and such plasticizers are preferably included from about 10 to 40 weight percent and more preferably from about 10 to 30 weight percent based on the weight of the composition absent the antimicrobial agent.

Additionally, the prepolymer compositions described herein preferably include a polymerization inhibitor and a polymerization initiator in effective amounts to prevent premature polymerization but provide for *in situ* polymerization on mammalian skin. For example, an effective amount of a polymerization inhibitor is preferably included in the composition to inhibit premature polymerization of the composition. Likewise, the polymerization initiator is included in the composition in effective amounts to initiate polymerization when the composition is placed under polymerization conditions (e.g., light). As above, such initiators include thermal initiators, light activated initiators and the like and *in situ* polymerization of the prepolymer composition on mammalian skin preferably occurs within 0.5 to 5 minutes.

The biocompatible prepolymer compositions may additionally contain one or more optional additives such as colorants, perfumes, rubber modifiers, tackifiers, modifying agents, etc. In practice, each of these optional additives should be both miscible/dispersible and compatible with the prepolymer composition and the resulting

polymer. Compatible additives are those that do not prevent the use of the prepolymers in the manner described herein.

In general, colorants are added so that the polymer layer formed on the skin will contain a discrete and discernable color. Perfumes are added to provide a pleasant smell to the formulation. Rubber modifiers are added to further enhance the flexibility of the resulting polymer layer. The amount of each of these optional additives employed in the composition is an amount necessary to achieve the desired effect.

When employed, each of these additives are incorporated into the composition and the resulting composition mixed until homogeneous.

Utility

The methods described herein are useful in forming *in situ* an antimicrobial adherent polymer film on the skin surface of a mammalian patient. Such mammalian patients preferably include humans as well as, for example, domestic animals exemplified by horses, cows, dogs, sheep, cats, etc. and any other mammalian species.

The polymer film finds particular utility in inhibiting microbial contamination thereunder and in the areas immediately adjacent thereto. Accordingly, such polymeric films can be used to topically cover small wounds on skin surfaces which wounds do not penetrate through the dermal layer of the skin as, for example, in the manner described in Barley, et al.[4] When so employed, the antimicrobial biocompatible prepolymer composition is applied over the wound. Upon polymerization, an antimicrobial polymeric film is formed over the wound which provides for antimicrobial properties at the wound surface while also preventing exogenous contaminants from entering the wound.

Additionally, the polymeric films formed from the antimicrobial prepolymer compositions described herein can also be used in the *in situ* formation of a surgical incise drape in the manner described by Askill, et al.[9] When so employed, the *in situ* formed film adheres to the mammalian skin surface to provide for a surgical incise drape which does not lift during surgery and has antimicrobial properties.

In any event, an antimicrobial polymeric drape is formed over the selected site by applying a biocompatible prepolymer composition of this invention to the skin surface at

the selected site. As noted above, this composition comprises polymerizable biocompatible monomers and/or reactive oligomers (prepolymers) which, upon application to the skin polymerizes *in situ* to form an antimicrobial biocompatible polymeric film.

Still further, the polymeric films formed from the antimicrobial prepolymer compositions described herein can be used in methods for treating active dermatoses (e.g., dermatitis, psoriasis and eczema).[19] In such methods a polymerizable prepolymer composition is applied to the topical surface of the dermatosis and then the prepolymer is polymerized *in situ* on this surface so as to form a coherent polymeric film over the dermatosis.

When so used, the antimicrobial polymeric film will only adhere to the skin for a period of about 1-4 days after which time it sloughs off. This occurs because the polymeric film adheres only to the uppermost portion of the epidermal layer which is continuously in the process of being sloughed off and replaced by the underlying cells. Accordingly, the antimicrobial polymeric film need not be removed after *in situ* formation. However, if immediate removal of the polymeric film is required, such can be removed with a suitable biocompatible solvent, e.g., acetone or isopropanol.

Kits

In view of the many different uses for topical application onto mammalian skin, this invention also encompasses a kit of parts useful for applying the antimicrobial prepolymer compositions described herein onto mammalian skin. In particular, such a kit of parts comprises (a) a container comprising therein an antimicrobial biocompatible prepolymer composition as described above and (b) an applicator means for applying the composition onto mammalian skin.

The container comprises any compatible material which stores the prepolymer composition without degradation of the container or prematurely polymerizing the prepolymer. Such materials include, by way of example, inorganic materials such as glass (including amber glass), metals, ceramics, and the like as well as organic materials such as polyolefins including fluorinated polyolefins, and the like.

Suitable applicator means include brushes, rollers, aerosols, swabs, wipes, and the like.

In one embodiment, the container and applicator means are combined into a single article such as a brush affixed to the terminal portion of the container wherein means are employed to prevent premature release of the prepolymer composition. For example, the brush may be overlaid with a removable impermeable barrier. When application of the prepolymer composition is intended, the barrier is simply removed. Alternatively, a frangible barrier may be used and broken or crushed to release the material for mixing prior to use.

In another embodiment, the container and applicator means are separate articles designed to mate with each other. For example, the prepolymer composition could be stored in an amber vial sealed with a screw cap and the applicator means includes a screw mechanism which mates with a complimentary screw mechanism on the top of the vial. When application of the prepolymer composition is intended, the cap is removed from the vial and the applicator is attached.

In still another embodiment, the container itself comprises a two-component system. Such two component systems can be used, e.g., with two-component epoxy prepolymer systems wherein the first component is segregated from the other. For example, a diepoxide composition is added to one component of the container and a diamine added to the other. At the time of use, the components are then mixed to provide for a polymerizable prepolymer composition of this invention.

Alternatively, the two-component system can be used to store the antimicrobial agent in one component of the container and the prepolymer composition in the other component. At the appropriate time, the components can be mixed to provide for a prepolymer composition of this invention. Multiple component systems can also be used (e.g., a three component system comprising a two component epoxy prepolymer composition and the antimicrobial agent each stored in separate compartments segregated from each other until time of use).

Kits similar to those described above have been described in U.S. Patent Application No. 08/962,868,[20] filed concurrently herewith, as Attorney Docket No.

026446-111 and entitled "*Kits Containing Cyanoacrylate Compositions Comprising an Antimicrobial Agent.*" This application is herein incorporated by reference in its entirety.

The following examples illustrates certain embodiments of the invention but is not meant to limit the scope of the claims in any way.

EXAMPLES

In the examples below, all temperatures are in degrees celsius (unless otherwise indicated) and all percents are weight percent (also unless otherwise indicated) except for percent inhibition which is true mathematical percentage. Additionally, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

CFU	=	colony forming units
g	=	grams
hrs.	=	hours
min.	=	minutes
ml	=	milliliters
mm	=	millimeters
SAB-DEX	=	Sabouraud Dextrose
TSA	=	trypticase soy agar

EXAMPLE 1

This example illustrates the preparation of two separate prepolymer compositions, one comprising chlorhexidine diacetate as the antimicrobial agent and the second comprising tetracycline hydrochloride as the antimicrobial agent. In this example, ambient conditions were employed unless otherwise noted.

Specifically, 47.5 g acrylate urethane prepolymer (available under the tradename LOCTITE 3104, from Loctite Corp., Rocky Hill, Connecticut) was combined with 2.5 g dimethylamino ethylacrylate and 0.25 g. camphorquinone (both available from Aldrich Chemical Co., Milwaukee, Wisconsin). This composition was covered to exclude light and then mixed until homogenous and the camphorquinone was dissolved. This composition is referred to as "Composition A."

0.5 g chlorhexidine diacetate (Aldrich) was added to 4.5 g of Composition A. This was covered to exclude light and mixed until a uniform dispersion was formed. This composition is referred to as "Composition B."

0.05 g tetracycline hydrochloride (Sigma Chemical Co., St. Louis, Missouri) was added to 4.95 g of Composition A, covered to exclude light and mixed until the tetracycline hydrochloride was dissolved. This mixture is referred to as "Composition C."

Small samples of approximately 1 to 2 g of each of Composition A, B, and C were placed between two approximately 4 by 6 inch sheets of PARAFILM (American National Can, Neenah, Wisconsin) and pressed to achieve approximately 3 inch zones of composition. These sheets were then exposed to white light of approximately 250 watts (halogen lamp) at a distance of about 12 inches, and cure times were measured. Compositions A and B cured within 30 seconds and Composition C cured within 60 seconds.

EXAMPLE 2

This example illustrates *in vivo* application onto mammalian skin of a prepolymer composition of Example 1.

Specifically, following the procedure of Example 1 above, an antimicrobial prepolymer composition is prepared containing chlorhexidine diacetate as the antimicrobial agent (such as Composition B, above). Approximately 2 g of this composition is applied onto the calf of a human female subject using a flat metal blade to spread the mixture into a smooth, flat film. This film is covered with a thin transparent plastic film (such as is used to wrap foods) and is exposed at about a 12 inch distance to white light of about 250 watts (halogen lamp) for sixty seconds. The polymeric film cures tack-free in about 2 minutes, at which time the transparent plastic film can be removed from the polymeric film. After about 1 to 3 days, the polymeric film will slough off the calf. The skin under the polymeric film is normal in appearance with no redness or irritation.

EXAMPLE 3

The following example illustrates how the antimicrobial effects of a polymeric film of this invention can be determined.

A. Preparation of the Inoculum

Specifically, the surfaces of two TSA plates, 100 x 15 mm, are inoculated with stock cultures (maintained on TSA slants) with the following microorganisms using a sterile inoculating loop: *Staphylococcus aureus* (ATCC No. 6538) and *Staphylococcus epidermidis* (ATCC No. 12228). The plates are incubated at 30° to 35°C for 24 hrs. The surfaces of two SAB-DEX agar plates are streaked with *Candida albicans* and incubated at 20-25°C for 48 hrs.

The cultures are harvested with sterile saline. Each culture suspension is collected in a sterile container and sufficient sterile saline is added to reduce the microbial count to obtain a working suspension of approximately 1 x 10^8 CFU's per ml.

The specific microorganisms recited above are selected for inclusion herein because they are common human skin pathogens (bacteria and fungus).

B. Inoculation of Plates

Each of the three test microorganisms is used to inoculate individual TSA plates by streaking them with sterile cotton tip applicators saturated with the appropriate suspension. The plates are allowed to dry.

C. Inhibition Study

Films of polymerized prepolymer comprising chlorhexidine diacetate or tetracycline hydrochloride are formed as in Example 1 and are cut into approximately 11 to 13 mm^2 pieces. The pieces are placed in the center of the appropriate inoculated TSA plates (the tetracycline hydrochloride film is not tested with *Candida albicans*). An untreated 25 mm filter disk is cut in half, and one half is placed in the center of the appropriate inoculated TSA plate while the other half is place in the center of non-inoculated TSA plates, to serve as a negative control. Two inoculated plates of each microorganism are also used as positive controls without the test article. These plates are then incubated for 3 days at 30° to 35°C. After incubation, the plates are removed and examined for any signs of microbial growth inhibition.

Zones of inhibition extending at least 1 mm from the antimicrobial films evidence that the antimicrobial is leaching from the film and imparting antimicrobial properties to the film.

From the foregoing description, various modifications and changes in the composition and method will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

Claims:

1. An antimicrobial prepolymer composition which comprises:

(a) a polymerizable biocompatible prepolymer composition; and

(b) an antimicrobially effective amount of an antimicrobial agent with the proviso that the biocompatible prepolymer composition is neither a cyanoacrylate prepolymer composition nor a silicone prepolymer composition and the antimicrobial agent is not a complex of iodine molecules.

2. The composition according to Claim 1 wherein the polymerizable biocompatible prepolymer, in monomeric form, is selected from the group consisting of urethane acrylate, (C_1-C_6 alkyl) methacrylate, (C_1-C_6 alkyl) acrylate, (C_1-C_6 hydroxyalkyl) acrylate, (C_1-C_6 hydroxyalkyl) alkacrylate, styrene, α-methyl styrene, vinyl acetate, one and two component epoxy materials and mixtures thereof.

3. The composition according to Claim 2 wherein the polymerizable biocompatible prepolymer is urethane acrylate.

4. The composition according to Claim 2 wherein the polymerizable biocompatible prepolymer is a (C_1-C_6 alkyl) methacrylate.

5. The composition according to Claim 2 wherein the polymerizable biocompatible prepolymer is (C_1-C_6 alkyl) acrylate.

6. The composition according to Claim 2 wherein the polymerizable biocompatible prepolymer is a (C_1-C_6 hydroxyalkyl) acrylate.

7. The composition according to Claim 2 wherein the polymerizable biocompatible prepolymer is (C_1-C_6 hydroxyalkyl) alkacrylate.

8. The composition according to Claim 2 wherein the polymerizable biocompatible prepolymer is styrene.

9. The composition according to Claim 2 wherein the polymerizable prepolymer is α-methyl styrene.

10. The composition according to Claim 2 wherein the polymerizable prepolymer is vinyl acetate.

11. The composition according to Claim 2 wherein the polymerizable prepolymer is selected from one and two component epoxy materials.

12. The composition according to Claim 1 wherein said antimicrobial agent is selected from the group consisting of antibacterials, anti-fungals, antibiotics, antivirals and antiparasitics.

13. The composition according to Claim 12 wherein said antimicrobial agent is selected from the group consisting of acyclovir, amphotericin B, bacitracin, butoconazole nitrate, carbol-fuchsin solution, chloramphenicol, chlortetracycline hydrochloride, ciclopirox olamine, clindamycin phosphate, clotrimazole, econazole nitrate, erythromycin, gentamycin sulfate, gentian violet, haloprogin, iodochlorhydroxyquin, ketoconazole, mafenide acetate, metronidazole, miconazole nitrate, mupirocin, naftifine, neomycin sulfate, nitrofurazone, nystatin, oxiconazole nitrate, silver sulfadiazine, sulconazole nitrate, tetracycline hydrochloride, tolnaftate, undecylenic acid and zinc undecylenate, benzyl benzoate, crotamiton, lindane, permethrin, pyrethrins, cetrimide, chlorophenols, chlorhexidine and pharmaceutically acceptable salts thereof.

14. The composition according to Claim 1 which further comprises a biocompatible plasticizer.

15. The composition according to Claim 1 which further comprises a polymerization inhibitor and a polymerization initiator.

16. A kit of parts comprising

(a) a container comprising therein an antimicrobial prepolymer composition which comprises:

(i) a polymerizable biocompatible prepolymer; and

(ii) an antimicrobially effective amount of an antimicrobial agent; and

(b) an applicator means for applying the composition onto mammalian skin.

17. A kit of parts according to Claim 16 wherein the container and applicator means are combined into a single article.

18. A kit of parts according to Claim 16 wherein the container and applicator means are separate articles.

19. A kit of parts which comprises:

(a) a first container comprising a polymerizable biocompatible prepolymer; and

(b) a second container comprising an antimicrobial agent.

20. The kit of parts according to Claim 19 wherein the first or second container further comprises an applicator means such that upon mixing of the prepolymer and the antimicrobial agent, the resulting composition can be applied to mammalian skin.

21. The kit of parts according to claim 19 which further comprises a separate applicator means.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/23213

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :B32B 3/16

US CL : 424/78 402, 467 ; 523 /122; 524 /54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/78 402, 467 ; 523 /122; 524 /54

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

ACS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	DD 298,251 A (BASF SCHWARZHEIDE GMBH) 23 December 1988, see entire document.	1-15 --- 1-15
X --- Y	JP 52-24234 A (SUMITOMO BAKELITE KK) 23 February 1977, see the abstact.	1-15 --- 1-10
X --- Y	JP 02-145675 A (NISSHIN HIGH VOLTAG) 05 June 1990, see the abstract.	1-15 --- 1-10
X --- Y	US 3,228,830 A (MCFADDEN et al) 11 January 1966, see col. 5,lines 25 et seq.	1-10 and 12-15 --- 1-10

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the *claimed* invention cannot be considered novel or cannot be considered to involve an *inventive* step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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INTERNATIONAL SEARCH REPORT

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PCT/US98/23213

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 4,880,617 A (CHROMCEKet al) 14 November 1989, see. col. 4,lines 30-47.	1,2,4-10,12 -17 and 19 ---------- 1,2, 4-10
X --- Y	US 5,578,662 A (BENNETT et al) 26 November 1996, see column 6, lines 39-44 and column 8, lines 6-31.	1,and 19 ---------- 12-15
X --- Y	US 4,882,166 A (GRAHAM et al) 21 November 1989, see column 7, line 51 et seq.	1 and 19 ---------- 12-17
Y	US 4,542,012 A (DELL) 17 September 1985, see columns 3 and .10	1-21